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Influence of admixed citric acid on the release profile of pelanserin hydrochloride from HPMC matrix tablets

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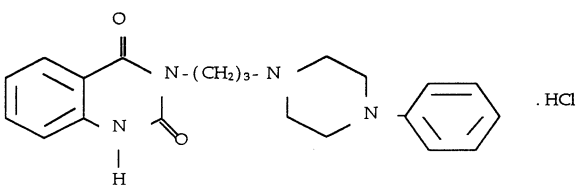
Abstract

Pelanserin is a weakly basic experimental drug with a short half-life and a prolonged release formulation was developed using hydroxypropyl methylcellulose (HPMC) and citric acid to set up a system bringing about gradual release of this drug. For this purpose powder mixtures were wet granulated with water and compressed with a hydraulic press at 55 MPa. Dissolution studies were made using 900 ml HCl 0.1 N, the first 3 h, and phosphate buffer pH 7.4, h 3–8. Dissolution curves were described by $M_t/M_{inf} = kt^n$, applied separately for each dissolution medium. The dissolution mechanism involved a coupled diffusion/relaxation with a trend favoring the diffusion mechanism with increasing citric acid concentrations. Increasing concentrations of citric acid produced increasing values of the kinetic constants, in a cubic relationship. Higher HPMC proportions produced slower dissolution rates but with a citric acid compensating more clearly a decreased solubility of pelanserin at pH 7.4. Individually calculated dissolution curves showed experimental 8 h pelanserin dissolution in a range of 65–99% for matrices with 100 mg HPMC/tab., while those with 200 mg HPMC/tab. were in the range 57–73%.

Keywords: Pelanserin; Release mechanism; HPMC, Sustained release; Citric acid; pH effect



1. Introduction

Pelanserin, 3-[3-(4-Phenyl-1-piperazyl) propyl]-1,2,3,4-tetrahydroquinazoline-2, 4-dione hydrochloride, is an antihypertensive experimental drug. This drug possesses several mechanisms of action and is effective in reducing blood pressure when administered orally. Because of this, pelanserin is considered to possess potential therapeutic usefulness in the treatment of arterial hy-

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pertension (Flores-Murrieta et al., 1992a). Pelanserin in humans is rapidly absorbed and eliminated from plasma (Flores-Murrieta et al., 1992b). When a drug has a relatively short elimination half-life, it is difficult to maintain the concentration within the therapeutic range without frequent dosing or the use of sustained release formulations. This makes pelanserin a candidate for a sustained release system.

The use of hydrophilic polymers is actually the most used method in controlling the release of drugs in the formulation of oral pharmaceutical dosage forms. Hydroxypropyl methylcellulose (HPMC) is a polymer frequently used in the formulation of controlled release dosage forms. The mechanisms by which it retards drug release include its ability to form rapidly a gel layer at the matrix periphery exposed to aqueous fluids (Mandal, 1995). The drug is released from the matrix mainly by diffusion through water filled pores. Consequently, the release rate is associated to porosity and tortuosity of the pores and channels network. The porosity and tortuosity of a swellable matrix are primarily attributed to polymer swellability (Efentakis et al., 1997).

Variables such as the particle size, viscosity and proportion of HPMC modify the characteristics of porosity and tortuosity of the swollen matrix and therefore, modify the release rate of drugs. Increasing proportions of HPMC in the matrix decreases the release rate (Campos-Aldrete and Villafuerte-Robles, 1991; Martini et al., 1995). An increasing particle size of HPMC produces increasing release rates from the tablets (Mitchell et al., 1993; Campos-Aldrete and Villafuerte-Robles, 1997) and decreasing release rates occur often with an increasing viscosity grade (Campos-Aldrete and Villafuerte-Robles, 1997; Kim and Fassihi, 1997).

Changing several formulation factors, such as type of excipients and manufacture processes can modify drug release from matrix tablets (Vázquez et al., 1992). Admixing another polymer may bring about different effects according to the type and strength of interactions between the polymers forming the gel barrier (Traconis et al., 1997).

The effect of adding non-polymeric excipients to a polymer matrix has been claim to produce increases in the release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipient is insoluble like tricalcium phosphate (Lapidus and Lordi, 1968).

The addition of excipients like mannitol and calcium phosphate (Emcompress) to matrix tablets showed different effects related mainly to the excipients solubility. Carteolol · HCl was released much faster from matrices containing mannitol (35%) compared with those matrices containing calcium phosphate (35%). This was attributed to the high solubility of lactose (Holgado et al., 1995). However, the effect of adding non-polymeric excipients (soluble and insoluble) was not always demonstrated (Veiga et al., 1997). The release profile of theophyline from hydrophilic HPMC matrices remained unchanged when lactose and tricalcium phosphate were added at concentrations of 11 and 22%.

Drug release from matrix systems is influenced by aqueous solubility of the drug. Moreover, the aqueous solubility of drugs considered weak bases exhibit decreasing magnitudes with an increasing pH of the solvent. Because of this, formulation of this type of drug for oral administration can be expected to result in decreasing release rates with increasing pH in the gastrointestinal tract (Van der Veen et al., 1991). Penetration of intestinal juices with pH higher than that in the stomach may cause a conversion of the more ionizable drug to a less soluble base. This conversion, total or partial, brings down the solubility and therefore the diffusion rate of the drug through the matrix. This effect is dependent of the pK_a of the drug and the pH of the intestinal fluids.

The addition of some organic acids to matrix tablets has been used to recover partially the release rate of drugs from non-swelling insoluble matrices. At a constant matrix composition, dissolution of tablets in phosphate buffer pH 7.4 showed that the release of ephedrine · HCl ($pK_a = 9.6$) was pH-independent while that of papaverine · HCl ($pK_a = 6.5$) was pH-dependant. The release of papaverine · HCl in buffer pH 7.4 was improved by the incorporation of organic acids (Gabr, 1992).

The aim of this work is to study, systematically and quantitatively, the possibilities of modulating the pelanserin hydrochloride release from HPMC matrices with the addition of different amounts of a hydrosoluble acidic excipient, citric acid. Moreover, to study the influence of the citric acid addition on the mechanisms of pelanserin release.

2. Materials and methods

2.1. Materials

The pharmaceutical excipients hydroxypropyl methylcellulose F4MP (Colorcon), anhydrous citric acid USP (Fisher Scientific Co.) and the experimental drug pelanserin hydrochloride (CINVESTAV-IPN, Mexico) were used as received.

2.2. Methods

2.2.1. Matrix preparation

Hydroxypropyl methylcellulose was used to produce matrices containing 20 mg pelanserin hydrochloride loading in different ratios of HPMC:citric acid. The powder (10 g) were mixed in a twin shell blender during 20 min at 18 rpm and then manually granulated with water, kneading 5 min. The wet mass passed through a number 14 sieve. The wet mass was kneaded 5 min again and passed finally through the sieve. The granules were dried at 40°C to get moisture not greater than 4%, determined by the Karl Fisher method (Aquatest 10). Tablets containing 20 mg pelanserin hydrochloride, 100 mg or 200 mg HPMC and 20, 40, 60, 80, 100 and 120 mg citric acid were prepared by compression of the granules in a hydraulic press with 8-mm flat faced punch and die, at a compaction pressure of 55 MPa.

2.2.2. Dissolution methodology

Dissolution studies were carried out at 37°C and 50 rpm, with the USP 23 dissolution apparatus II (paddle method) (Hansen Research) in 900 ml dissolution medium. For the first 3 h the dissolution medium was HCl 0.1 N and then, for the following 5 h, the pH of the medium was adjusted to pH 7.4 by adding 5.0 g of NaOH and 6.12 g of potassium phosphate dissolved in 40 ml water. This new volume was considered to calculate the percentage of pelanserin dissolved.

Samples (3.0 ml) were withdrawn at predetermined time intervals, filtered and analyzed spectrophotometrically at a wavelength of 218 nm (Beckman DU-650 spectrophotometer). Dissolution medium (3.0 ml) was added to maintain a constant volume.

3. Results and discussion

3.1. Pelanserin hydrochloride release from matrices with 100 mg HPMC/tab

In general, the release data from swellable systems can be analyzed according to the power law expression shown in Eq. (1), when delay in release or lag time do not exist (Vogireaux and Ghaly, 1994; Mandal, 1995):

$$M_t/M_{\inf} = kt^n \quad \text{or} \quad \ln(M_t/M_{\inf}) = n\ln(t) + \ln(k) \tag{1}$$

The terms in this equation are as follows: M_t, the amount of drug released at time t; $M_{\inf}$, the total drug released over a long time period; k, the kinetic constant; and n, the mechanism of drug release. The value of n ranges from 0.5 ($t^{1/2}$ dependence, generally referred to as Fickian release) to 1 (representing the case II transport which is purely relaxation controlled). The values in between indicate an anomalous behavior corresponding to coupled diffusion/relaxation.

Release data of pelanserin hydrochloride from matrices containing the various citric acid concentrations produced straight-line plots with Eq. (1). When the regressions were calculated for a drug release in a time up to 8 h. The correlation coefficients for most of the data were >0.99 (Table 1).

However, the change or adjustment of pH after 3 h slowed down the release rate, changing the release profile. A better fit could be obtained by calculating the regression divided into two parts, like by the curve containing 20 mg citric acid per

Table 1
Regression parameters of the pelanserin dissolution curves from HPMC matrices (100 mg/tab.), using first HCl 0.1 N as medium (up to 3 h) and then phosphate buffer pH 7.4 (h 3–8)[a]

Citric acid	Slope (n)	Intercept	R^2	k	$M_{8\,h}$ (%)[b]
20	0.7160	−1.754	0.992	0.1730	76.68
40	0.7264	−1.737	0.995	0.1761	79.76
60	0.6509	−1.479	0.990	0.2279	88.21
80	0.6771	−1.542	0.997	0.2139	87.43
100	0.6750	−1.398	0.989	0.2471	100.55
120	0.6325	−1.206	0.987	0.2994	111.54

[a] $\ln(M_t/M_{inf}) = \text{Slope}*\ln t + \text{Constant}$.
[b] Calculated values from individual regressions. $k = 6.7177 \times 10^{-8} \times \text{citric acid}^3 + 0.1834$; $R^2 = 0.895$.

tablet (Fig. 1). The regression parameters for all curves corresponding to matrices containing 100 mg HPMC/tab. are given in Table 2, for the release profile in HCl 0.1 N (0–3 h), and in Table 3, for the release profile in phosphate buffer pH 7.4 (h 3–8).

In general, is clear a decrease in pelanserin release rate when the pH of the medium was changed from that of HCl 0.1 to pH 7.4. This is supposed to be due to a change in solubility of pelanserin from 2817 to 231 μg/ml. This could be accounted for by the conversion, total or partial, of pelanserin hydrochloride to the less soluble pelanserin free base, after the change in pH, in spite of the possible contribution to pH of citric acid. The effect of this change in solubility is a decreased diffusion of pelanserin through the gel barrier.

3.1.1. Significance of citric acid loading dose on release kinetics

Citric acid loading in the range of 20 to 120 mg/tab., while keeping the drug and polymer content constant, significantly affected the release process. As the content of citric acid was increased the ability to sustain drug release decreased. The increase in the citric acid content from 20 to 120 mg/tab. increased the amount pelanserin dissolved after 3 and 8 h (Tables 2 and 3). At a time of 3 h the amount dissolved increased from 43 to 68% and after 8 h from 65 to 99%. These results indicate an early begin of citric acid release that increased the dissolution rates from the first and along the whole process. The citric acid effect could be considered to be the sum of two concepts. In a first approach, citric acid could act recovering a drop in solubility after the change in pH, because of its contribution to maintain a low pH inside the matrix (Gabr, 1992). In a second approach, citric acid may act loosening the matrix structure through an increased porosity created after its dissolution and release. As can be observed in Fig. 1, the citric acid effect can not be explained with the first approach because pelanserin release from HPMC matrices without citric acid and dissolving in HCl 0.1 N produced a lower release, $M_{3\,h} = 27.2\%$, than ma-

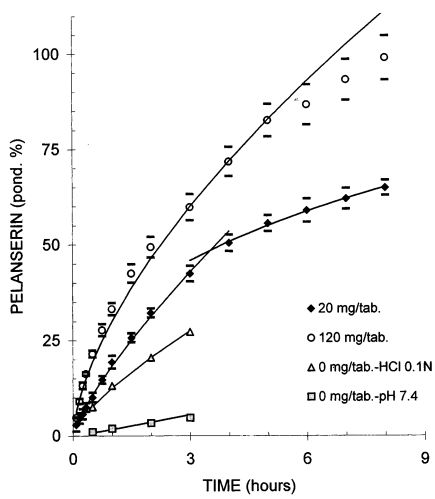

Fig. 1. Dissolution of pelanserin from HPMC matrices (100 mg/tab.) containing different amounts of citric acid (0–3 h, HCl 0.1 N; 3–8 h, phosphate buffer pH 7.4). Averages of three repetitions, standard deviation and regression in one and two parts.

Table 2
Regression parameters of the pelanserin dissolution curves from HPMC matrices (100 mg/tab.), in their first part, using HCl 0.1 N as medium and covering the time up to 3 h[a]

Citric acid	Slope (n)	Intercept	R^2	k	$M_{3\,h}$ (%)[b]
20	0.7739	−1.6975	0.9962	0.1831	42.835
40	0.7734	−1.6905	0.9991	0.1844	43.156
60	0.7277	−1.4055	0.9975	0.2453	54.257
80	0.7101	−1.5098	0.9980	0.2209	48.207
100	0.7427	−1.3288	0.9916	0.2648	59.880
120	0.6933	−1.1434	0.9865	0.3187	68.268

[a] $\ln(M_t/M_{inf}) = \text{Slope}*\ln t + \text{Constant}$.
[b] Calculated values from individual regressions. $k = 7.263 \times 10^{-8} \times \text{citric acid}^3 + 0.1935$; $R^2 = 0.873$.

trices with 20 mg citric acid/tab., $M_{3\,h} = 42.8\%$. Because of this, it is considered that the main effect is derived from the second approach. The effect of citric acid seems more the effect of a hydrosoluble excipient than an acidic one. A fast release of this excipient, in a time shorter than 3 h, would increase the porosity and decrease the tortuosity and therefore would allow a faster release rate.

About the first approach, citric acid is used in pharmaceutical products as acidulant to adjust the pH and as synergistic antioxidant. The pH of a 0.1 N aqueous solution of citric is 2.2 (The Merck Index, 1983). It could be considered that citric acid would maintain a low pH in the matrix microenvironment, independently of the pH of the biological fluids. In this manner, increasing the solubility and the dissolution rate of pelanserin. The quantitative chemical basis of a possible enhanced dissolution of pelanserin in an acid medium is derived from the buffer or Henderson–Hasselbach equation. In this case the solubility of pelanserin in HCl 0.1 N is high (2817 μg/ml), while in phosphate buffer pH 7.4 is quiet lower (230 μg/ml). This circumstance provides a much higher dissolution in HCl 0.1 N, according to the Noyes–Whitney equation (Martin et al., 1983). However, it is clear a decrease in solubility after 3 hours dissolution. Citric acid is not recovering the reduction in dissolution at pH 7.4, probably because of an early dissolution of citric acid, before the change in pH occurs. The maintenance of an acid medium in the matrix is dependent of a sustained release of the acid. This seems not to be the case, according to the curves of Fig. 1. These figures show a higher dissolution from matrices containing citric acid (20 mg HPMC/tab.) than those containing no-citric acid but dissolving in HCl 0.1 N.

About the second approach, it can be considered that swellable systems, like those made of HPMC particles, are based in polymers which swell rather fast and with release kinetics which is controlled predominantly by the pore network rather than the polymer (Peppas, 1987). To obtain a particular release rate from these systems, the first though would be to manipulate the porosity or the drug loading of the matrix (Carstensen, 1987). In swellable systems it is visualized that the dispersed drug or particles of drug and excipient can not delocalize their positions in the polymer matrix. It is believed that the drug and excipient molecules can elute out the matrix only by disso-

Table 3
Regression parameters of the pelanserin dissolution curves from HPMC matrices (100 mg/tab.), in their second part, using phosphate buffer pH 7.4 as medium, covering the time of h 3–8[a]

Citric acid	Slope (n)	Intercept	R^2	$M_{8\,h}$ (%)[b]
20	0.3589	−1.1748	0.9955	65.156
40	0.3708	−1.1495	0.9944	68.499
60	0.3945	−1.0903	0.9951	76.056
80	0.4704	−1.2064	0.9948	79.583
100	0.4394	−1.0463	0.9882	87.588
120	0.4458	−0.9345	0.9847	99.257

[a] $\ln(M_t/M_{inf}) = \text{Slope}*\ln t + \text{Constant}$.
[b] Calculated values from individual regressions.

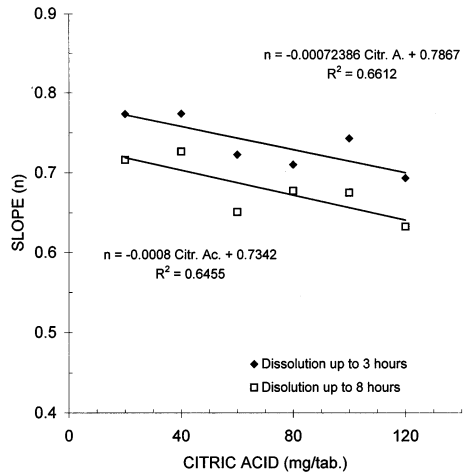

Fig. 2. Relationship between the regression slopes (n) of the dissolution curve and the citric acid content of pelanserin–HPMC matrices (100 mg/tab.).

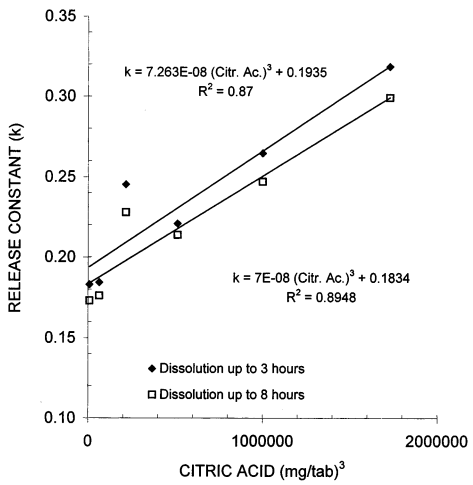

Fig. 3. Relationship between the kinetics or the release constant of pelanserin dissolution curves from HPMC matrices (100 mg/tab.) and their citric acid content.

lution in and then by diffusion through the pore network. The porosity and the thickness of the depletion zone become greater as more solids elute out the device.

Citric acid is a high water soluble material, circa 67% w/w (The Merck Index, 1983) or 210% w/v (Van der Veen et al., 1991) at 37°C. The granulation with water of a water-soluble excipient, like citric acid, will dissolve it in a variable degree. The part dissolved of this excipient is then distributed on the surface of the non-dissolving particles. After drying the part dissolved remains as a solid layer deposited around the non-dissolving particles, in this case on HPMC particles. The rest of the particles of the soluble excipient remain random distributed after this process (List et al., 1980).

Taking in account the granulation process, it is believed that citric acid acts loosening the matrix structure through an increased porosity created after its dissolution and release. Moreover, it is also believed that citric acid acts loosening the structure by separation of HPMC particles, after dissolution of the citric acid deposited around them.

The slopes or n values calculated for the complete dissolution process were between 0.72 and 0.63 (Table 1 and Fig. 2), while those calculated for pelanserin dissolution in HCl 0.1 N were between 0.77 and 0.69 (Table 2 and Fig. 2). These data indicate that the drug release mechanism may be attributed to an anomalous transport for all cases, as would be expected for swellable matrices. There is a linear trend to decreasing values of the exponent n as the matrices citric acid content increases (Fig. 2). Matrices possessing greater proportions of citric acid exhibit a drug release closer to a diffusion-controlled process.

Mechanistically, matrices with high citric acid content show a smaller dependence of the drug released on polymer relaxation. Maybe due to a faster penetration of the water front and hence to a faster hydration and establishment of a looser gel barrier from the first, after dissolution and release of citric acid. This citric acid deposited on the HPMC particles, during granulation, and localized also as discrete crystals between HPMC particles. Matrices with swelling restrictions, like those with lower citric acid proportions, exhibit a shift towards drug release by relaxation mechanism (Vogireaux and Ghaly, 1994).

Matrices with low citric acid content would result in a more concentrated gel and increased gel tortuosity. Thus, the diffusional path would become more convoluted and the diffusion rate would therefore decrease. The effect of an increased tortuosity and a delayed water penetra-

tion is shown in Fig. 3. This is expressed as slowed release constants, considering the dissolution up to 3 h as well as up to 8 h. There is a linear relationship between the cube of the citric acid content and the release constant (k). This meaning that lower tortuosities and higher water penetration would be the result of an increase in the volume of added citric acid.

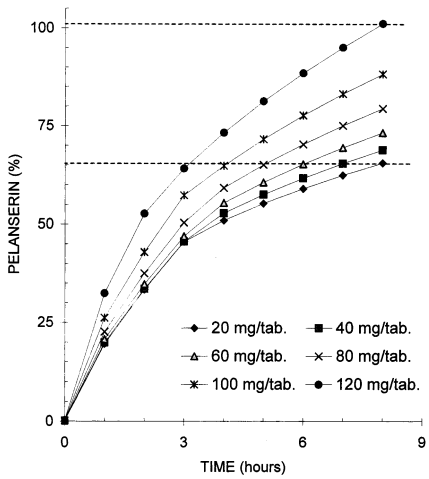

Fig. 4. Calculated response surface curves for the effect of the citric acid content on the dissolution of pelanserin from HPMC matrices (100 mg/tab.).

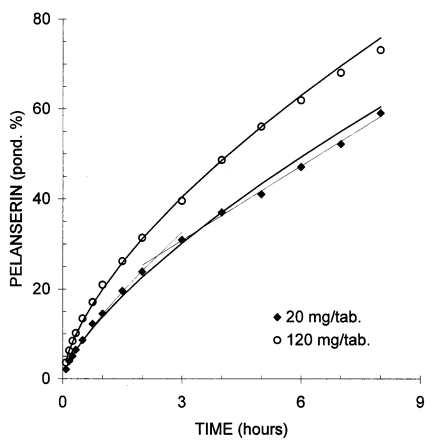

Fig. 5. Dissolution of pelanserin from HPMC matrices (200 mg/tab.) containing different amounts of citric acid (0–3 h, HCl 0.1 N; 3–8 h, phosphate buffer pH 7.4). Regression in one and two parts.

Linear relationships, between the slope (n) of release curves in Tables 2 and 3 and the citric acid content so as between the intercepts and the cube of the citric acid content, allowed the estimation of the response surface curves shown in Fig. 4. These curves indicate the range of possibilities of controlling the sustained release of pelanserin from matrices made of 100 mg HPMC per tablet and different amounts of citric acid.

3.2. Pelanserin hydrochloride release from matrices with a HPMC content of 200 mg/tab

Dissolution profiles of pelanserin matrices containing 200 mg HPMC/tab. are shown in Fig. 5. The regression parameters of the curves of this series, here omitted, were similar to those presented for matrices containing 100 mg HPMC/tab. The release mechanisms seem to be the same as by tablets containing 100 mg HPMC. However, the curves calculated ignoring a decreased solubility because of the pH change deviate in a smaller proportion from experimental points, compared to matrices with 100 mg HPMC/tab. This meaning that these matrices almost overcame the drop in solubility produced by the pH change after 3 h dissolution. Although a small effect can be still observed on the dissolution curves, this becomes smaller with increasing concentrations of citric acid (Fig. 5). The results obtained from matrices made of 200 mg HPMC/tab. could be attributed to a slower release rate of citric acid and in this manner, decreasing and extending gradually its effect through a longer period of time, producing a lower curvature of the curves.

The average slope (n) of the whole release process of matrices containing 200 mg HPMC/tab. (0.716) showed a little greater value than matrices with 100 mg HPMC/tab. (0.679, Table 1). This indicates a greater dependence of matrices containing 200 mg HPMC/tab of the mechanism of relaxation/erosion for the release of pelanserin. Greater HPMC proportions restrict the solvent penetration and the citric acid release so that the establishment of a stable fully hydrated gel barrier requires more time. Consequently, making the dissolution process more dependent of the mechanism of relaxation.

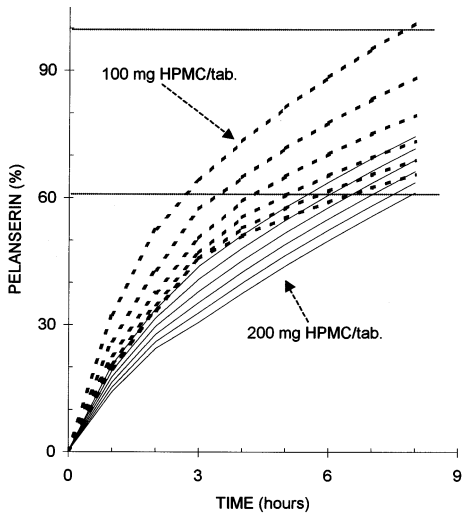

Fig. 6. Comparative calculated response surface curves for dissolution of pelanserin from two different size HPMC matrices, with a citric acid content in the range 20–120 mg/tab.

The restricting effect of an increased HPMC proportion decreased the release constants making them also less sensible to variations in the citric acid content. In the case of matrices with 200 mg HPMC/tab. the best fit for the relationship between the k values and the citric acid content was a linear one instead of the cubic relationship used in the case of matrices with 100 mg HPMC/tab. Fig. 6 shows the calculated response surface curves for the dissolution of pelanserin from 200 mg HPMC matrices. These curves exhibit a narrower range of variation of the sustained release of pelanserin obtained through addition of different amounts of citric acid, compared to those with 100 mg HPMC/tab.

Concluding, the use of HPMC matrices makes possible a sustained release of pelanserin with a coupled dissolution mechanism of diffusion/relaxation. There is a trend favoring the mechanism of diffusion with the addition of increasing quantities of citric acid. The addition of citric acid to HPMC matrices produces greater dissolution rates according to the citric acid content. This effect is considered mainly due to a loosening of the matrix after dissolution and release of its citric acid content. The citric acid effect is reduced in magnitude and extended in time by a double increase of the HPMC proportion, this favoring a more gradual release of pelanserin. The citric acid effect is based mainly on the degree of looseness of the matrix as well as on the speed of this process. The dissolution and release of citric acid occurs presumably in a time not longer than 3.

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